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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of:	Pettis *et al.*	Confirmation No.:	4392
Application No.:	10/028,989	Art Unit:	3763
Filed:	December 28, 2001	Examiner:	Williams, Catherine Serke
For:	METHOD AND DEVICE FOR REDUCING THERAPEUTIC DOSAGE	Attorney Docket No.:	11219-023-999 (P-4901P4)

DECLARATION OF DR. RONALD J. PETTIS
UNDER 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, DR. RONALD J. PETTIS, do hereby declare and state:

1. I am a co-inventor of the subject matter disclosed and claimed in the above-identified patent application (herein referred to as "the '989 application").

2. I am currently Technology Manager at Becton, Dickinson and Company, Inc. which is the assignee of the '989 application.

3. My academic background, technical experience and list of publications are set forth in my *curriculum vitae*, attached hereto as Exhibit A.

4. I have reviewed the claims of the '989 application as amended in the concurrently filed Amendment under 37 C.F.R. § 1.111. I have also reviewed U.S. Patent No. 5,527,288 to Gross *et al.* (herein referred to as "Gross").

5. The presently claimed invention of the '989 application relates to a method for delivering a substance to a specific depth of a human subject's skin through a hollow needle

having an outlet depth and exposed height which are located within the intradermal compartment so that an improved systemic bioavailability of the substance is achieved. The claimed method specifies placement of a needle within the subject's skin so that neither the needle's outlet depth nor its exposed height are outside the intradermal compartment. By using the claimed method, a person of ordinary skill in the art achieves control of the resulting pharmacokinetic profile through intradermal administration of a substance, *e.g.*, insulin. In contrast, failure to place the needle within the specified depth in the skin or use of a needle with an exposed height outside the intradermal compartment will not achieve the same result as the claimed methods. Placement of the outlet's depth and exposed height above the intradermal compartment would result in leakage of the injected substance up and out of the injection site; while placement of the outlet's depth and exposed height below the intradermal compartment would result in delivery to the subcutaneous compartment.

6. The intradermal delivery method claimed in the '989 application is distinct from Gross's purported intradermal delivery method. A careful reading of Gross indicates that while there might be some overlap in terms of needle length with the '989 application (*see*, Gross at col. 4, lines 18-22), the reference as a whole fails to teach how to specifically deliver a substance into the intradermal compartment in order to achieve the improved pharmacokinetic parameters as claimed in the '989 application. Critical features of the invention of the '989 application are simply absent from Gross. Unlike Gross, the '989 application teaches the importance of not only the needle length but also proper positioning of the needle outlet's exposed height into the intradermal compartment of the subject's skin. There is absolutely no disclosure in Gross concerning the height and depth of the needle outlet or the criticality of its placement within the intradermal compartment. Gross does not describe insertion of a needle so that both the depth and exposed height of its outlet (*i.e.*, orifice) are located within the intradermal compartment of the subject's skin. This feature,

however, is a requirement specified in Claims 69 and 85 of the '989 application. Nor does Gross disclose the use of intradermal administration as a means of controlling drug pharmacokinetics; further, Gross fails to differentiate intradermal administration from subcutaneous administration.

7. In addition to its effect on a substance's pharmacokinetic profile, such as insulin, further evidence of the significance of accurately placing the needle outlet's depth and exposed height in the intradermal compartment is shown by the outcome of pharmacodynamic studies conducted with insulin. Studies describing the pharmacodynamic response upon administration of insulin to animals in accordance with the claimed invention are described below in paragraphs 8-15.

8. I describe below the results of time course studies of blood glucose concentrations in rabbits upon administration of insulin in accordance with the claimed invention. I designed the studies described herein, which were conducted under my direction, and I am familiar with the results. The studies demonstrate that when insulin is administered in accordance with the claimed method at the same concentration (100 IU/mL) and at the same rate (0.1 mL/h) as described in Example 1 of Gross (*see*, col. 10, line 61 to col. 11, line 7) a very different pharmacodynamic result is achieved. The different result could only result from a different method of delivery. In fact, as a result of intradermal administration of insulin in accordance with the claimed method at 100 IU/mL, the blood glucose concentrations of the test animals dropped to levels which could not be reversed by ceasing administration of insulin, nor by intervening through administration of glucose to the hypoglycemic test animals. If Gross had been practicing intradermal delivery as claimed in the '989 application, the same result would have been observed; it was not.

9. We administered two different insulin types in the studies, whereas Gross does not disclose what type of insulin is administered. In one study, designated Study 1, we

administered to rabbits regular human insulin (Lilly Humulin®). In the other study, designated Study 2, we administered to rabbits a fast acting human insulin analog (Lilly Lispro®) reported to have a faster onset of, and shorter duration of action than human insulin.

10. We administered 100 IU/mL solution of insulin at a rate of 0.1 mL/h for two hours. We injected insulin in accordance with the invention at three different depths; at 1 mm, at 2 mm, and at 3 mm. The 1 and 2 mm depths are within the range of 0.5-2.0 mm for the penetration depths described at p. 13, lines 10-11 of the '989 application.

11. We injected the rabbits on the right/dorsal flank region using Becton Dickinson single needle catheter sets having a 34 gauge needle. We used a Harvard Apparatus PHD 2000 Program Pump having qualified accuracy for both volume and rate of delivery.

12. In order to further confirm that insulin administered by the method described in paragraphs 10-11 above was injected in the intradermal compartment, in Study 1, we also assessed blood glucose concentrations in a rabbit in which insulin was delivered beneath the surface of the skin into the intradermal compartment using a narrow gauge needle of 1.5 mm length inserted at a shallow angle to the skin to further reduce the depth of administration. We also determined blood glucose concentrations in a rabbit which was not administered with insulin as a negative control in Study 1.

13. For each rabbit in both studies, we analyzed the blood glucose concentrations from blood samples withdrawn from the ear vein using a 25 gauge needle. We sampled the rabbits at 0, 15, 30, 45, 60, 75, 90, 105, 120, 150, 180, 210, and 240 minutes. We determined blood glucose concentrations on two different Accuchek Glucose Meters, and averaged the results for each time point.

14. **Results** - Exhibits B and C present the results of Study 1 (using regular human insulin), and Exhibits D and E present the results of Study 2 (using the fast-acting human

insulin analog). Exhibits B and D show the average blood glucose levels in mmol/L over the time course of the studies. Exhibits C and E show the results of the studies, wherein the blood glucose concentrations are normalized to the starting time (time=0) concentration for each rabbit, and thus, present the results obtained for each time point as a percentage of the starting blood glucose concentration.[1] For comparative purposes, the graphs in Exhibits B, C, D, and E superimpose the data reported directly from Figure 12 of Gross.

15. **Results** - All rabbits receiving insulin in the studies experienced more precipitous drops in blood glucose concentrations and lower maximal glucose concentrations than reported in Gross.[2] These observations held for administration of insulin at all three depths (1 mm, 2 mm, and 3 mm) as well as for insulin administered using the 1.5 mm length needle in Study 1. In fact, all rabbits receiving insulin in the studies had to be humanely euthanized between 2 and 2.5 hours due to seizures caused by severe hypoglycemia, or due to two consecutive blood glucose concentration readings of $\leq$ 10 mg/dL.[3] The severe hypoglycemia experienced by the rabbits could not be reversed by ceasing administration of insulin, nor by administration of glucose. Administration of either type of insulin, *i.e.*, human insulin (in Study 1) and human insulin analog (in Study 2), in accordance with the claimed invention resulted in more precipitous drops in blood glucose concentrations and lower maximal glucose concentrations than reported in Gross.

16. I declare further that all statements made in this Declaration of my own knowledge are true, and that all statements made on information and belief are believed to be true, and further, that these statements were made with the knowledge that willful false statements and that like so made are punishable by fine or imprisonment, or both, under

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[1] Presentation of the blood glucose concentration as a percentage change from the starting blood glucose concentration, rather than the absolute blood glucose concentration, facilitates comparison of the blood glucose changes across the population of rabbits used in the study.

[2] Based on tissue site biopsies, the average skin thickness of the rabbits used in the studies was 1.5 mm.

[3] Humane euthanasia endpoints occurred per an institutional animal care and use committee.

Section 1001 of Title 19 of the United States code and that such willful false statements may jeopardize the validity of this application and any patent issuing thereon.

Dated: June 7, 2007

RONALD J. PETTIS